General

Guideline Title

Diagnosis and management of acute graft-versus-host disease.

Bibliographic Source(s)

Dignan FL, Clark A, Amrolia P, Cornish J, Jackson G, Mahendra P, Scarisbrick JJ, Taylor PC, Hadzic N, Shaw BE, Potter MN, on behalf of the Haemato-oncology Task Force of the British Committee [trunc]. Diagnosis and management of acute graft-versus-host disease. Br J Haematol. 2012 Jul;158(1):30-45. [137 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Note from the British Committee for Standards in Haematology (BCSH): The BCSH guidelines on graft-versus-host disease have been split into three documents, which are designed to be used together and to complement each other in order to provide an evidence-based approach to managing this complex disorder. In addition to the current document, the following National Guideline Clearinghouse (NGC) summaries are available:

- Diagnosis and management of chronic graft-versus-host disease
- Organ-specific management and supportive care in graft-versus-host disease

Definitions for the quality of the evidence (A-C) and strength of recommendation (strong [grade 1], weak [grade 2]) are given at the end of the "Major Recommendations" field.

Diagnosis

- An accountable transplant physician should be responsible for supervising the treatment of patients with acute graft-versus-host disease (GvHD) (1C).
- Clinical criteria should define acute GvHD and not purely time post-transplant (1B).
- Clinical diagnosis is appropriate if the classical constellation of symptoms is present. Biopsies may be helpful if diagnosis is unclear but should not delay management (1A).

Grading

- At diagnosis, the extent of individual organ involvement and overall grade of acute GvHD should be documented, taking into account all

organ involvement, as this has prognostic significance (1A).
- The modified Seattle Glucksberg criteria (Przepiorka et al., 1995) are recommended for grading (1A).

Management of Acute GvHD

Management of Grade I Disease

- The management of grade I disease should include topical therapy and optimizing levels of calcineurin inhibitors without the need for additional systemic immunosuppression (1C).

First Line Treatment of Grade II–IV Disease

- The use of systemic corticosteroids is recommended for first line therapy for grade II–IV GvHD (1A).
- Two milligram/kg per day of methylprednisolone is recommended as the starting dose for patients with grades III–IV GvHD (1A).
- One milligram/kg per day of methylprednisolone is recommended for patients with grade II GvHD (2B).
- The use of 'nonabsorbable' steroids can be considered for acute intestinal GvHD in order to reduce the dose of systemic steroids (2B).

Second Line Treatment

- The following agents are suggested for use in the second line treatment of steroid-refractory acute GvHD: extracorporeal photopheresis, anti-tumour necrosis factor α antibodies, mammalian target of rapamycin (mTOR) inhibitors, mycophenolate mofetil, interleukin-2 receptor antibodies (2C).

Third Line Treatment

- The following agents are suggested as third line treatment options in acute steroid-refractory GvHD: alemtuzumab, pentostatin, mesenchymal stem cells and methotrexate (2C).

Definitions:

Quality of Evidence

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomized clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomized clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series, or just opinion.

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Clinical Algorithm(s)

The original guideline document contains clinical algorithms for:

- Initial treatment of acute graft-versus-host disease (GvHD)
- Treatment for grade III–IV GvHD

Scope

Disease/Condition(s)

Acute graft-versus-host disease (GvHD)

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Allergy and Immunology

Endocrinology

Hematology

Oncology

Pediatrics

Intended Users

Physicians

Guideline Objective(s)

To provide an evidence-based approach to diagnosis and management of acute graft-versus-host disease

Target Population

Adults and children (unless otherwise specified in the original guideline document) in the United Kingdom with acute graft-versus-host disease (aGvHD) following allogeneic stem cell transplant

Note: The guideline does not cover the diagnosis and management of patients with transfusion-related GvHD.

Interventions and Practices Considered

Diagnosis/Evaluation/Risk Assessment

1. Management by an accountable transplant physician
2. Diagnosis of acute graft-versus-host disease (aGvHD) by clinical criteria
3. Biopsy if diagnosis is unclear
4. Evaluation of all organ systems (to assess prognosis)
5. Grade determination with the modified Seattle Glucksberg criteria

Treatment/Management

1. Treatment of grade I aGvHD
    - Topical corticosteroid therapy
    - Optimization of calcineurin inhibitor dose
2. First line treatment with systemic corticosteroids
    - Systemic corticosteroids for grade II-IV aGvHD
    - Dose of initial methylprednisolone based on grade of aGvHD
    - 'Nonabsorbable' (budesonide, beclomethasone) for acute intestinal aGvHD for systemic corticosteroid dose reduction
3. Second line treatment of steroid-refractory acute aGvHD
    - Extracorporeal photopheresis
    - Anti-tumour necrosis factor α antibodies
    - Mammalian target of rapamycin (mTOR) inhibitors
    - Mycophenolate mofetil
    - Interleukin-2 receptor antibodies
4. Third line treatment for steroid-refractory aGvHD
    - Alemtuzumab
    - Pentostatin
    - Mesenchymal stem cells
    - Methotrexate

Note: The following treatments were discussed and not recommended: rituximab, visilizumab, anti-CD147 antibody (ABX-CBL), thalidomide, azathioprine and intra-arterial methylprednisolone.

Major Outcomes Considered

- Specificity of clinical diagnostic symptoms
- Differential diagnosis of acute graft-versus-host disease (aGvHD)
- Effectiveness of biopsy to confirm aGvHD
- Timing of appearance of symptoms
- Correlation of outcome with grade of aGvHD
- Complete and partial response rates to treatment
- Incidence of chronic GvHD
- Mortality
- Side effects and complications of treatments

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The production of these guidelines involved a literature review to 17 June 2011 including Medline, internet searches and major conference reports.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomized clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomized clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series, or just opinion.

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

The production of these guidelines involved the following step:

- The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The production of these guidelines involved the following steps:

- Establishment of a working group comprising experts in the field of allogeneic transplantation followed by literature review.
- Development of key recommendations based on randomized, controlled trial evidence. Due to the paucity of randomized studies some recommendations are based on literature review and a consensus of expert opinion.
- The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used assess the strength of recommendations. The GRADE criteria are specified in the British Committee for Standards in Haematology (BCSH) guideline pack and the GRADE working group website (see the "Rating Scheme for the Strength of Recommendations" field). Further information is available from the following websites:
  - http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html
  - http://www.gradeworkinggroup.org/index.htm

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The production of these guidelines involved the following steps:

- Review by the British Committee for Standards in Haematology (BCSH) committees, the British Society of Blood and Marrow Transplantation (BSBMT) executive committee, the UK Photopheresis Society and the UK Paediatric Bone Marrow Transplant Group
- Review by sounding board of the British Society for Haematology (BSH) and allogeneic transplant centres in the UK

Evidence Supporting the Recommendations

References Supporting the Recommendations

Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, Thomas ED. 1994 consensus conference on acute GVHD grading. Bone Marrow Transplant. 1995 Jun;15(6):825-8. [11 references] PubMed

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate diagnosis and management of patients with acute graft-versus-host disease (GvHD), which may lead to effective control of GvHD while minimizing the risk of toxicity and relapse

Potential Harms

- The toxicities of treatment may be different in a growing child with a developing organ system and these side effects should be considered

when choosing a treatment option.

- In view of the risk of haemolytic uraemic syndrome and hyperlipidaemia, mammalian target of rapamycin (mTOR) inhibitors should be used with caution in combination with calcineurin inhibitors. mTOR inhibitors also have a number of other drug interactions and a dose reduction may be required when used in combination with certain drugs including all azole antifungal agents. When used in combination with azoles, the initial dose of sirolimus should be reduced by 40%–50%. Regular monitoring of drug levels is recommended to avoid toxicities.
- Prolonged use of topical steroids can thin skin and may cause erythema, striae and dyspigmentation. If more than 50 g of very potent steroid is used per week, sufficient steroid may be absorbed through the skin to result in adrenal gland suppression or Cushingoid features.
- Extracorporeal photopheresis (ECP) has an excellent safety profile. The side effects appear to be mild and include hypotension, fevers and reduced haemoglobin level.
- There are reports of an increased risk of infection in patients treated with infliximab.

Qualifying Statements

Qualifying Statements

- Recommendations in these guidelines are applicable to adults and children unless otherwise specified. The doses in the guidelines are for adults and the equivalent paediatric doses would need to be calculated according to the unit policy of the paediatric transplant centre. The following issues are particularly important in paediatric practice:
  - A substantial number of children undergo transplants for non-malignant disorders and will not benefit from the graft-versus-malignancy effect. This may have implications for the choice of graft-versus-host disease (GvHD) therapy.
  - There may be a variety of co-morbidities due to the underlying disease which may alter the appearance of GvHD.
  - The toxicities of treatment may be different in a growing child with a developing organ system and these side effects should be considered when choosing a treatment option.
- While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology, the British Society of Blood and Marrow Transplantation nor the publishers accept any legal responsibility for the content of these guidelines.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Dignan FL, Clark A, Amrolia P, Cornish J, Jackson G, Mahendra P, Scarisbrick JJ, Taylor PC, Hadzic N, Shaw BE, Potter MN, on behalf of the Haemato-oncology Task Force of the British Committee [trunc]. Diagnosis and management of acute graft-versus-host disease. Br J Haematol. 2012 Jul;158(1):30-45. [137 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Jul

Guideline Developer(s)

British Society for Haematology Guidelines - Professional Association

British Society of Blood and Marrow Transplantation - Professional Association

Source(s) of Funding

British Committee for Standards in Haematology

Guideline Committee

Joint Working Group of the British Committee for Standards in Haematology (BCSH) and the British Society of Blood and Marrow Transplantation (BSBMT)

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Financial Disclosures/Conflicts of Interest

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Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the British Committee for Standards in Haematology Web site .

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on July 30, 2012. The information was verified by the guideline developer on September 5, 2012.

Copyright Statement

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